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THE LEUKOCYTIC PICTURE IN INFLUENZA.

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THE two recent epidemics of influenza have given opportunity for restudying the blood changes in this disease. Yet such study, judging from the reports, has been for the most part incidental to a general clinical study and has not been sufficient to establish the leukocytic picture in the infection. At least I have found but one paper, that of Adler,¹ of Zurich, in which the blood findings have been a matter of primary interest and have received adequate consideration.

In the text-books on clinical diagnosis and on medicine commonly available to students the notes on the leukocytic picture of influenza are hazy and contradictory. These books, as a matter of course, have not had the benefit of the findings in the recent epidemics. Further, in many cases, their statistics seem to have been compiled from single counts in a patient, without reference to the day of the disease, or without accurate determination of the presence or absence of complications in the patient. Thus, Cabot² states that five-sixths of his cases had a normal leukocyte count, and of the eleven with leukocytosis one or more had complications. Emerson³ reports that after an early low leukocyte count one-half of his cases showed a count of over 10,000 cells, some even reaching a count of 20,000. Yet in his statement that "influenza covers a wide group

¹ *Folia Hæmatologica*, November, 1919, xxv, 16.

² *Clinical Examination of the Blood*, 2d edition, 1898, p. 214.

³ *Clinical Diagnosis*, 2d edition, 1908, p. 528.

of cases," one has evidence that at the time of publication (1908) he did not have a clear-cut idea as to the specificity of the infection. Simon⁴ states that in uncomplicated cases the leukocytes are commonly diminished but may be normal, and that with a count of over 15,000 cells some complication is present. During the course of the disease he records a lymphocytosis with low neutrophile and eosinophile values, and a return of neutrophile values to normal with convalescence. Webster⁵ states that there is usually a diminution in white cells, though a normal count may be found. Bass and Johns⁶ tabulate little or no increase in leukocytes, with a differential increase in both neutrophiles and small mononuclears. Sahli⁷ makes no note of the blood picture because of the vague conceptions of the disease. The blood changes are apparently considered by some to have no importance in diagnosis, as no note is found concerning them in Albutt, in *Monographic Medicine*, or in Musser. Lord,⁸ in Osler's *Modern Medicine*, reports that in 167 cases representing the simple acute form of the disease with slight respiratory disturbance the leukocytes did not exceed 12,000 in 70 per cent., and in the other 30 per cent. the greater leukocytosis could not be accounted for by complications. With deeper involvement of the respiratory tract, one-half of 54 cases with bronchitis and two-thirds of twelve cases with pneumonia gave a count of more than 12,000.

In the journal reports of the 1918 epidemic, chiefly from the army camps, the statements of blood-findings are much sharper and show closer agreement.⁹ Keeton and Cushman found a leukopenia (with a minimum count of 900 cells) in 46.6 per cent. of their cases and a normal count in 24.7 per cent.; in the cases with recovery after bronchopneumonia there was a leukocytosis in 62.2 per cent.; and in the bronchopneumonia cases with fatal outcome a leukocytosis in but 41.3 per cent. Brem, Bolling and Casper¹⁰ found a leukopenia practically always, in the influenzal stage, and they concluded that the initial infection produced a depression of the bone-marrow, but that the latter was capable of stimulation in secondary pyogenic infection. Ross and Hund¹¹ found a leukopenia with a count from 1800 to 3000 in their desperately ill influenza-pneumonia cases. Dever, Boles and Case¹² found a tendency toward leukopenia well marked in some cases of uncomplicated influenza and a leukocytosis in the majority of the cases with a complicating pneumonia. Zeedick¹³ found a normal count or a leukopenia in most of the uncomplicated cases and is much inclined to the opinion that any count above normal means a secondary bacterial invasion. In his

⁴ Clinical Diagnosis, 6th edition, 1907, p. 100.

⁵ Diagnostic Methods, 3d edition, 1913, p. 499.

⁶ Laboratory Diagnosis, 1917, p. 57.

⁷ Clinical Diagnosis, 2d edition, (Potter), 1911, p. 801.

⁸ Modern Medicine, 1907, ii, 481.

⁹ Jour. Am. Med. Assn., 1919, lxxii, 640.

¹⁰ Ibid., 1918, lxxi, 2138.

¹¹ Ibid., 1919, lxxii, 640. ¹² Ibid., 1919, lxxii, 265.

¹³ Studies in Epidemic Influenza, Univ. of Pittsburgh, 1919.

opinion leukocytosis at the end of the course is not a part of the blood picture, but there is instead a gradual return to the normal count in convalescence; while with pneumonia there is, as a rule, a very moderate leukocytosis if there is not a leukopenia. Kinsella and Broun¹⁴ have emphasized, in addition to these leukocyte pictures, the great reduction in blood-platelets that occurs in the disease.

Adler,¹⁵ whose paper came to hand after the completion of the study to be reported here, has attempted to construct the leukocytic picture of the disease by daily total and differential counts on the patients. He finds an increase in leukocytes during the prodromal stage and on the first febrile day. This is followed by a leukopenia, with reduction in neutrophiles, eosinophiles and basophiles which is due to marrow inhibition. This is succeeded by a positive marrow reaction, until, on the fourth or sixth day, the blood-picture approaches the normal. There is also an early absolute reduction in number of lymphocytes, followed by a reactive lymphocytosis. Adler insists that a disease with a constant leukocytosis cannot be influenza. He draws a further sweeping conclusion, possibly not entirely justified, that diseases which result in immunity show in their course a leukopenia, diseases without an immunity a leukocytosis. Two apparently striking exceptions, scarlet fever and smallpox, he explains on the dominance of the picture by the secondary streptococcal invader.

One may summarize these more recent reports by stating that in influenza there is an early inhibition (not exhaustion) of the marrow activity by the infecting agent, resulting in a leukopenia which is characteristic of the disease. The marrow is capable of stimulation upon pyogenic infection as a complication, and there results a leukocytosis usually of moderate degree.

During the 1920 epidemic of influenza among the students of the University of Wisconsin the author made a daily study of the differential leukocyte picture in a short series of cases treated in the University Infirmary. This study was made with no thought of a publication of statistical results, but merely with the hope that it might throw some light on the nature of the disease and on some of its phenomena. I realize the series of cases is short and publication is hardly justified from the standpoint of statistics. Yet conclusions that may be drawn from the uniformity of findings (within the limits of individual variation), and, further, certain practical points in the care of patients, indicated by the blood findings, seem to justify reporting the work. I wish to express here my indebtedness to Dr. W. S. Middleton for the clinical notes, and to Miss Hazel Gray for the great majority of the total leukocyte counts.

In the hope of obtaining the leukocytic picture of the primary infection, cases were selected which showed no signs of deep respiratory infection upon admission. As it happened no case which was

¹⁴ Jour. Am. Med. Assn., 1920, lxxiv, 1070.

¹⁵ Loc. cit.

selected terminated fatally, but several cases did show complications in the course of the disease. Some had very mild attacks and were sent from the hospital to their rooms as soon as afebrile, but before their blood picture had returned to normal. This was necessitated by the extent of the epidemic and the demand for beds for the very sick, and is not to be construed as the general practice in regard to the student sick or as a practice to be recommended. In fact, the main practical point that comes from a study of the blood picture in influenza is that patients should be carefully attended until the blood does return practically to normal.

In making the daily differential counts it has been thought sufficient to count 200 cells, if the two hundreds, as such, did not materially differ from each other in proportion of cells. If there was marked difference an increased number was counted. It is realized that in single counts no number less than 500 cells will give an accurate percentage for the cells which exist in the circulation in small proportion, as the eosinophiles and basophiles. In repeated counts, however, and where the main interest is in the cells largely represented, as neutrophils and lymphocytes, the smaller number gives close accuracy in well-made cover-slip smears. The cells have been classed into seven groups: neutrophils, eosinophiles, basophiles, small lymphocytes, large lymphocytes, large mononuclear cells and transitionals. But one or two of these groups need explanation. The cell classified as a large lymphocyte is the lymphocyte with considerable protoplasm which has usually a somewhat acidophilic reaction and contains commonly a few coarse azurophile sometimes rod-like granules when stained by Wright's stain. This has been considered by the author to be a more mature small lymphocyte and is found normally in the blood stream. The large mononuclear is a large cell with round or oval nucleus and has been considered an immature form of the so-called transitional which has a polymorphous nucleus. If we may trust the oxidase reactions these are both chiefly of marrow origin in the normal blood.

The cases and their blood counts follow. The first group of five cases consists of those with light attacks and with no pulmonary complications.

CASE I.—Mr. E.

1920.	Total count.	Neutrophils.		Eosinophiles.		Basophiles.		Small lymphocytes.		Large lymphocytes.		Large mononuclears.		Transitionals.	
		Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.
Jan. 21	13,000	76.5	9945	0.0	0.0	0.5	65	9.6	1235	1.5	195	0.0	0.0	12	1560
22	7,000	35.5	2485	1.0	70	1.5	105	39.5	2605	2.5	175	1.0	70.0	19	1330
23	6,800	42.0	2856	3.5	238	1.5	102	36.5	2482	4.0	272	0.0	0.0	125	1250

Blood-platelets distinctly fewer than normal on all smears. Patient admitted with temperature of 102.8° on the morning of January 21. Afebrile on January 22; discharged January 24. No pulmonary symptoms or findings, no complications.

CASE II.—Miss H. G.

1920.	Total count.	Neutrophils.		Eosinophiles.		Basophiles.		Small lymphocytes.		Large lymphocytes.		Large mononuclears.		Transitional.	
		Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.
Jan. 25	7800	79.0	6162	0.0	0.0	0.0	0.0	12	936	0.5	39	0.0	0.0	7.5	555
26	5000	58.5	2925	0.5	25.0	0.5	25.0	25	1250	3.0	150	0.0	0.0	12.5	625
27	4200	46.5	1953	0.5	21.0	2.0	84.0	32	1344	4.0	168	0.5	21.0	14.5	609

Blood-platelets distinctly diminished after the first day. Patient admitted during evening of January 24 with temperature of 103.2°; afebrile on January 28.

CASE III.—Miss H.

1920.	Total count.	Neutrophils.		Eosinophiles.		Basophiles.		Small lymphocytes.		Large lymphocytes.		Large mononuclears.		Transitional.	
		Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.
Jan. 20	5500	58.0	3190	0.0	0.0	0.0	0.0	20.3	1116	4	22	2.3	127	6.3	347
21	5200	55.5	2886	0.5	26	0.0	0.0	32.5	1690	4	208	1.0	52	6.5	343
22	6000	70.0	4200	0.0	0.0	0.0	0.0	20.5	1230	1	60	0.0	0.0	8.5	510

Platelets extremely few until January 22. Patient admitted January 20 with temperature of 100°. Afebrile afternoon of January 21. No complications or pulmonary signs. Discharged January 23. In the confusion attendant upon the rush of patients on January 20, a number of the total leukocyte counts were not recorded. In this case there was evidently a leukopenia or normal count, judging from the differential.

CASE IV.—Mr. M.

1920.	Total count.	Neutrophils.		Eosinophiles.		Basophiles.		Small lymphocytes.		Large lymphocytes.		Large mononuclears.		Transitional.	
		Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.
Jan. 25	6800	61.5	4182	0.0	00	0.0	00	23.0	1564	2.0	136	0.0	00	13.5	918
26	6200	36.5	2263	0.5	41	0.5	31	44.5	2759	6.5	403	1.5	93	10.0	620
27	8400	43.0	3612	0.5	42	0.0	00	37.0	3118	12.0	1008	3.0	252	4.5	378

Platelets few after January 25. Patient admitted evening of January 24 with temperature of 101.2°. Afebrile afternoon of January 26. Discharged January 28. No complications and no signs of pulmonary involvements.

CASE V.—Dr. M.

1920.	Total count.	Neutrophils.		Eosinophiles.		Basophiles.		Small lymphocytes.		Large lymphocytes.		Large mononuclears.		Transitional.	
		Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.
Jan. 25	7300	70.0	5110	0.0	00	1.0	73	16.5	1204	4.0	292	0.0	00	8.5	621
26	6000	52.5	3150	2.5	150	1.0	60	24.5	1470	6.5	390	0.0	00	13.0	780
27	6400	59.5	3808	6.0	384	0.5	32	18.0	1152	6.0	384	0.0	00	10.0	640

Platelets few throughout. Pseudopodial forms noted. Patient admitted on second febrile day. Afebrile after noon of January 26. Discharged evening of January 27. No complications or pulmonary signs.

In this group of mild attacks of the disease there was a moderately sharp fever on the first day of definite illness, and a rapid decline of temperature, with recovery on the third or fourth day, without complications. From the standpoint of the leukocytes it is evident that there may be a moderate leukocytosis at the outset of the attack. Even without a definite or marked increase in total leukocytes there is a relative neutrophile leukocytosis in those cases seen early enough. This is followed by a sharp drop in total leukocyte count due, in chief, to a pronounced fall in the number of polymorphonuclear neutrophiles, the total number of which per unit of circulation may be but from 25 to 50 per cent. of that on the previous day. The lymphocytes, on the other hand, show both a relative and absolute increase in number. Large mononuclears and transitionals vary slightly in reaction in the different cases, there being either a slight fall in number or practically a constant number. Eosinophiles and basophiles are either absent from the circulation or present in very small numbers. Blood-platelets show a sharp decrease, as estimated from the blood smear. In Case III they were extremely few, and the formation of platelet-like bodies from the large lymphocytes, as reported in another paper,¹⁶ was noted.

On the third day of disease in these mild cases we find, except in one case, a slight increase in total number of neutrophiles; some variation in the lymphocyte numbers, but usually an indication that the peak of reaction has been passed; little change in the large mononuclear group; a low count of eosinophiles in three cases, with a slight eosinophilia in two.

The next two cases ran a somewhat more severe course but without any pneumonia patches, although one had bronchial rales throughout.

CASE VI.—Miss E. H.

1920.	Total count.	Neutrophiles.		Eosinophiles.		Basophiles.		Small lymphocytes.		Large lymphocytes.		Large mononuclears.		Transitionals.	
		Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.
Jan. 21	10,600	73.5	7791	0.5	53	0.5	53	13.5	1431	2.0	212	0.0	00	10.0	1060
22	4,400	41.5	1826	0.0	00	0.5	22	36.5	1606	2.0	88	1.0	44	17.5	770
23	6,400	49.0	3136	0.0	00	0.5	32	31.0	2176	1.5	96	2.0	128	13.0	830
25	6,200	43.0	2666	0.0	00	0.0	00	45.0	2790	2.0	124	1.5	93	8.5	527
26	8,000	48.5	3880	0.0	00	0.5	40	35.5	2840	5.5	440	2.5	200	8.0	640
27	4,600	38.0	1748	0.5	23	0.5	23	43.0	1978	5.5	253	1.0	46	11.5	539

Platelets numerous January 21, then diminished until January 25, when increase apparent. Patient admitted January 21 with temperature of 102.4°. Gradual decline until January 25 when afebrile. No complications. Discharged January 27.

CASE VII.—Miss E.

1920.	Total count.	Neutrophiles.		Eosinophiles.		Basophiles.		Small lymphocytes.		Large lymphocytes.		Large mononuclears.		Transitionals.	
		Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.
Jan. 20	...	53.0	...	0.5	...	0.5	...	21.5	...	13.5	...	0.5	...	10.5	...
21	6200	40.5	2511	0.5	31	0.0	00	31.0	2108	13.0	716	0.5	31	11.5	713
22	3100	41.0	1304	1.0	34	0.0	00	37.0	1258	10.5	357	0.5	17	10.0	340
23	3600	43.5	1566	1.0	36	0.0	00	32.5	1160	11.0	396	1.5	54	10.5	378
24	2600	42.0	1092	0.0	00	1.0	26	37.0	962	10.5	273	0.5	13	9.0	234
25	9000	47.5	4275	0.0	00	0.0	00	30.0	2700	11.5	1035	1.0	90	10.0	900
26	6000	52.0	3120	0.5	30	0.0	00	30.5	1830	9.5	570	2.5	150	5.0	300
27	...	50.0	...	0.0	00	0.5	00	32.0	...	5.0	...	1.5	...	5	0

Platelets relatively few throughout. Patient admitted January 19 with evening temperature of 101°. Temperature ranged between 101.4° and 99° until January 26 when afebrile. No complications beyond the presence of rales at left apex from onset. Moderately severe course. Discharged January 27.

In these two cases we have the same features as shown in the earlier cases, but they are more pronounced, especially as far as the fall in neutrophile leukocytes is concerned. This leukopenia is also more persistent.

The following cases developed pneumonic patches and other complications during the course of their illness, but showed eventual recovery.

CASE VIII.—Miss V.

1920.	Total count.	Neutrophiles.		Eosinophiles.		Basophiles.		Small lymphocytes.		Large lymphocytes.		Large mononuclears.		Transitionals.	
		Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.
Jan. 21	6,600	71.0	4,686	0.0	00	0.5	33	8.5	561	3.0	198	1.5	99	15.0	990
22	4,400	30.5	1,342	0.0	00	0.5	22	35.0	1,540	1.0	44	2.5	110	21.5	946
23	9,600	66.0	6,336	1.0	96	0.5	48	16.0	1,536	7.0	672	1.0	96	8.5	816
24	5,400	71.0	3,834	0.0	00	0.0	00	14.0	756	3.5	189	0.5	27	11.0	594
25	9,600	73.5	7,056	0.0	00	0.0	00	6.0	576	5.0	480	0.5	48	15.0	1,440
26	14,000	76.0	10,640	0.0	00	0.0	00	7.5	1,050	1.5	210	2.0	280	13.0	1,820
27	19,400	80.5	15,617	0.0	00	0.0	00	8.5	1,649	0.0	00	0.5	97	10.5	2,037
28	16,000	79.5	12,720	0.0	00	0.0	00	6.0	960	3.0	480	0.0	00	11.5	1,840
29	17,800	73.0	12,994	0.0	00	0.0	00	7.0	1,246	2.5	445	0.0	00	17.5	3,115
30	15,000	70.5	10,545	0.0	00	0.0	00	8.5	1,275	2.5	375	0.5	75	18.0	2,700
31	14,200	67.5	9,585	0.0	00	0.5	71	12.5	1,775	3.0	426	0.0	00	16.5	2,343
Feb. 1	14,400	74.0	10,656	1.0	144	0.5	72	10.0	1,440	1.0	144	0.0	00	13.5	1,944
2	21,000	80.5	16,905	0.5	105	1.0	210	9.0	1,890	2.0	420	0.0	00	7.0	1,470
3	9,200?	76.0	6,992	0.5	46	0.5	46	12.5	1,150	0.5	46	0.5	46	9.5	874
4	17,400	79.0	13,746	1.0	174	0.5	87	7.5	1,305	3.0	502	0.0	00	9.0	1,566

Platelets relatively few until January 27 increasing afterward to an apparent maximum on February 3 and 4. Patient admitted January 21 with temperature of 103.4°. Temperature normal January 22. On January 23 temperature rose to 100.8° in the afternoon, when a pleuritic friction rub was heard and patches of consolidation made out in the lower right lobe. Thereafter there was irregular fever with a maximum of 104.8° on January 28. Temperature declined from this point, but persisted until February 3. An otitis media had developed and the ear drum was incised on February 1.

CASE IX.—Mr. S.

1920.	Total count.	Neutrophiles.		Eosinophiles.		Basophiles.		Small lymphocytes.		Large lymphocytes.		Large mononuclears.		Transitionals.	
		Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.
Jan. 24	6,600	41.0	2,706	0.5	33	0.5	33	36.0	2376	9.0	594	2.0	132	11.0	726
26	5,200	43.0	2,236	0.0	00	0.0	00	32.5	1690	7.0	364	1.0	52	16.5	858
28	5,400	31.0	1,836	1.5	81	0.0	00	42.0	2268	6.5	351	1.0	51	15.0	810
29	17,200	80.0	13,760	0.0	00	0.5	86	8.0	1376	2.5	431	0.5	86	8.5	1462
30	12,600	73.0	9,198	0.0	00	0.0	00	13.0	1638	3.0	378	0.5	63	10.5	1323
31	16,200	73.5	11,907	1.0	162	0.0	00	12.0	1944	0.5	81	0.0	00	13.0	1106

Platelets distinctly few until January 29, remaining above normal thereafter. Patient admitted on January 24 with temperature of 102°. Temperature normal on January 27 and 28. On January 29 temperature rose to 102.2° and a patch of decreased resonance and increased fremitus was found in the lower right lobe. Temperature normal on February 1; rose again on February 3, when patient was found to have parotitis. Eventual recovery.

CASE X.—Miss K.

1920.	Total count.	Neutrophiles.		Eosinophiles.		Basophiles.		Small lymphocytes.		Large lymphocytes.		Large mononuclears.		Transitionals.	
		Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.
Jan. 20	...	71.0	...	0.0	..	1.5	..	14.5	..	6.0	..	0.0	..	7.0	..
21	...	57.0	...	1.0	..	0.0	..	27.0	..	7.5	..	1.5	..	6.0	..
23	6,200	66.5	4123	0.0	00	0.0	00	21.0	1302	6.5	403	1.5	62	5.0	310
24	5,200	61.0	3328	0.0	00	0.5	26	24.0	1248	3.5	182	0.5	26	7.5	390
25	8,400	76.5	6426	0.0	00	0.0	00	15.0	1260	3.0	252	3.0	252	2.5	210
26	10,600	57.0	6042	0.0	00	0.5	53	28.0	2968	5.0	530	0.5	53	9.0	951
29	12,200	68.0	8296	0.5	61	0.0	00	17.5	2135	5.0	610	1.0	122	8.0	978

Platelets relatively few until January 29. Patient admitted January 19, with temperature of 101.2° with rates at both bases posteriorly. On January 21, a patch of consolidation in the lower right lobe was diagnosed. On January 25 consolidation was found at both bases. Temperature was normal on January 27. Convalescence was delayed by the development of new areas of consolidation in the right infrascapular region on February 5, with new febrile reaction which persisted until February 11. Recovery.

In two of these we have a characteristic behavior of the leukocytes in the early phases of the disease. The neutrophiles reach a low level in the circulating blood. Clinically the patients' temperature reached normal, and one might have expected immediate recovery; but there is a return of fever and, coincidentally, a change in leukocytic picture to a neutrophile leukocytosis and an area of pulmonary consolidation is discovered. After a period of irregular but fairly high leukocytosis there is recovery. Case X, with a somewhat irregular leukocytic picture, yet with early characteristics that indicate its etiology, shows a much feebler response to the pulmonary infection, and clinically the case had a longer course.

There is a consistency in these blood findings which would seem to justify certain conclusions, if not from these cases alone, at least when they are taken in conjunction with the work of others. They show that uncomplicated influenza has a characteristic blood picture. The features of this are an early neutrophile leukocytosis followed by a sharp drop to a leukopenia, with a marked deficiency in cells of marrow origin and of blood platelets and with a lym-

phocytosis of varying degree. There is a gradual return toward a normal picture, but a cessation of fever and of symptoms may occur with the presence of a very abnormal blood count.

This leukopenia suggests somewhat that of typhoid fever and also somewhat that of measles. It indicates sharply that the primary infecting agent is not a pyogenic coccus. The leukopenia in influenza would appear to depend upon a marrow inhibition like that in typhoid fever and not upon a severe injury to the marrow or to its exhaustion for in both diseases, given a pyogenic stimulation of the marrow through secondary infection, there is immediate response with a neutrophile leukocytosis, at least in reactive individuals. Even in other cases, as in the last of the series, with low total count, marrow response is shown in the relative neutrophile increase. What the nature of this marrow inhibition or negative chemotaxis may be is not evident.

This great poverty in circulating neutrophilic leukocytes would seem to account for the frequency of pyogenic complications in influenza. The complications in Cases VIII and IX have followed directly upon a very low neutrophile blood content. These cases, taken in conjunction with observations in measles and other conditions in which there is a similar low content of neutrophiles and succeeding pyogenic complications, suggest strongly that there is a danger limit of neutrophile reduction beyond which we become a prey to coccus infection—either from those we harbor or from those received from others by contagion. This is the basis for the point emphasized earlier, that in practice, influenza patients should not be allowed to get up and resume their ordinary life immediately upon the cessation of fever, but should be kept quiet and isolated until their blood has approached at least the normal leukocytic formula, which apparently requires almost a week from the cessation of fever.

The great platelet decrease in the blood in influenza, apparent in blood-smears, but established by the actual counts of Kinsella and Broun,¹⁷ is apparently responsible for the hemorrhagic character of the pneumonic exudate in that complication of the disease. Given endothelial injury through the secondary infection, one would expect a much prolonged bleeding time as a result of this platelet deficiency, also some deviation from normal in coagulation.

In view of the blood changes there arises an interesting theoretical question as to the nature of the cellular defense (if such there be) against the invading virus. Conquest of the infecting agent clearly is not brought about through the agency of the neutrophile leukocytes, as they remain particularly low throughout the uncomplicated attack. There is often, and probably, as a rule, a sharp lymphocytosis, but evidence from this series is not sufficient to credit this cell absolutely with the destruction of the infecting agent and the establishment of the immunity that is acquired.

¹⁷ Loc. cit.